

### REMARKS

Claims 1 – 4 and 6 – 12 are currently pending, with Claim 1 being the only independent claim. In the Office Action, the status identifier for Claim 12 was objected to. On the merits, Claims 1, 2, 10, and 12 were rejected under 35 U.S.C. § 102(b) as allegedly anticipated by U.S. Patent Number 5,500,416 to Miyazawa et al. (“Miyazawa”). Claims 1 – 4, 6, and 8 – 12 were rejected under 35 U.S.C. § 102(c) as allegedly anticipated by PCT Publication WO 2004/015124 to Menart et al. (“Menart ’124”). Finally, Claim 7 was rejected under 35 U.S.C. § 103(a) as allegedly obvious from Menart ’124 combined with Vuillard et al., Biochemistry Journal 305: 337 – 343 (1995) (“Vuillard”).

Each of the above-mentioned rejections is respectfully traversed. Favorable reconsideration is requested in view of the above amendments and following remarks.

I. Objection to Claim 12.

The Examiner first objected that the status identifier for Claim 12 was incorrect. In response, the status identifier for Claim 12 has been changed herein from “Currently Amended” to “Previously Presented.”

II. The Miyazawa Rejections.

The Examiner again contends that Claims 1, 2, 10, and 12 are anticipated by U.S. Patent Number 5,500,416 to Miyazawa et al. (“Miyazawa”). In order to address these contentions, Applicants submit herewith the Rule 132 Declaration of Dr. Vladka Gaberc-Porekar, a research scientist with at least ordinary skill in the relevant art, and one of the co-inventors of the present application.

As explained by Dr. Gaberc-Porekar in her Declaration, Claims 1, 2, 10, and 12, are directed to a pharmaceutical composition for parenteral administration which comprises an active pharmaceutical ingredient and a non-detergent sulfobetaine (NDSB). The claims further specify, among other things, that the NDSB is a quaternary ammonium salt having a nitrogen atom and four groups R1, R2, R3, and R4 – SO<sup>+</sup><sub>3</sub> bound to the nitrogen atom, wherein R1, R2 and R3 can be the same and/or different and are selected from the group consisting of one or more of methyl, ethyl, propyl, butyl, pentyl, hexyl and derivatives thereof, and R4 is (CH<sub>2</sub>)<sub>n</sub>,

wherein n is from 1 to 6. In other words, the NDSB does not have any carbon chains longer than six carbon atoms in length. (Gaberc-Porekar Declaration, ¶ 3).

The present inventors have surprisingly determined that NDSBs such as those specified in the claims may be beneficially used as excipients in final pharmaceutical formulations, particularly in formulations intended for parenteral administration. In these formulations, the NDSBs may function as a stabilizer, a buffering agent, and/or a pH adjusting agent. (Gaberc-Porekar Declaration, ¶ 4)

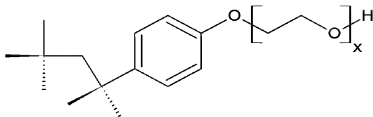
In sharp contrast to the present invention, Miyazawa discloses sulfobetaines said to be “amphoteric surfactants” at Column 3, lines 23 – 32 and Column 4, lines 32 – 42. “Amphoteric surfactant” sulfobetaines are clearly distinct from the non-detergent sulfobetaines (NDSBs) called for in the present claims. (Gaberc-Porekar Declaration, ¶ 5)

This should be evident to the Examiner as a person trained in the relevant art. A “non-detergent” form of a substance is very plainly diametrically opposed to a “surfactant” form of the substance. Everyone of ordinary skill knows that a “surfactant” is a “detergent” material. The terms “surfactant” and “detergent” are synonymous. (See attached exemplary materials from a Google search, confirming this fact). It is equally plain that a “non-detergent” form of a material is not a surfactant form of the material.

As Applicants have stressed before, the sulfobetaines in Miyazawa are “amphoteric surfactants.” Again, surfactants or detergents are water-soluble amphipathic molecules that possess both a hydrophobic group and a hydrophilic group that allow them to act as excellent solubilization agents. Surfactant molecules contain a hydrophilic polar head group from which extends a long hydrophobic carbon tail. The amphipathic properties of the surfactant molecules allow them to exhibit unique properties in aqueous solutions. The polar (hydrophilic) head groups interact with the hydrogen bonds of the water molecules and the hydrophobic tails aggregate resulting in highly organized spherical structures called micelles. (Gaberc-Porekar Declaration, ¶ 6)

Dr. Gaberc-Porekar cites several representative examples of amphoteric surfactants in her Declaration which are reproduced below:

Octylphenolpoly(ethyleneglycolether)



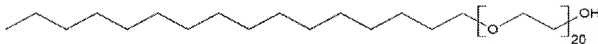
Molecular Formula:  $C_{34}H_{62}O_{11}$  for  $x=10$

Molecular Weight: 647 (for  $x=10$ )

Aggregation number: 100-155

Average micellar weight: 80,000

Polyoxyethylene (20) cetyl ether



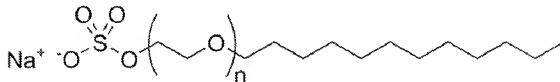
Molecular Formula:  $C_{16}H_{33}(OCH_2CH_2)_{20}-OH$

Molecular Weight: 1122

Aggregation number: 70

Average micellar weight: 79,000

Sodium Dodecyl Sulfate



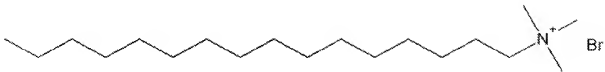
Molecular Formula:  $C_{12}H_{25}NaO_4S$

Molecular Weight: 288.38

Aggregation number: 62

Average micellar weight: 18,000

Hexadecyltrimethylammonium bromide



Molecular Formula:  $\text{CH}_3(\text{CH}_2)_{15}\text{N}(\text{Br})(\text{CH}_3)_3$

Molecular Weight: 364.5

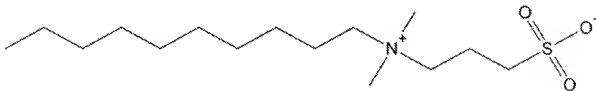
Aggregation number: 61 in  $\text{H}_2\text{O}$ ; 169 in 13mM KBr

Average micellar weight: 62,000

As is readily apparent from the foregoing structural formulas, each of these surfactants has a long hydrophobic carbon tail (substantially longer than six carbon atoms in length) and a correspondingly relatively high molecular weight, from about 300 daltons up to over 1000 daltons. Moreover, individual molecules of these surfactants are observed to aggregate in micelles containing dozens or even hundreds of similar molecules. The overall weight of these aggregated micelles can range from 10,000 up to 100,000 daltons. (Gaberc-Porekar Declaration, ¶ 7)

Dr. Gaberc-Porekar also cites particular examples of surfactant sulfobetaines in her Declaration, including the following:

N-Decyl-N,N-dimethyl-3-ammonio-1-propanesulfonate



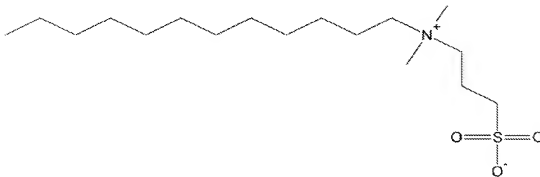
Molecular Formula:  $\text{CH}_3(\text{CH}_2)_9\text{N}^+(\text{CH}_3)_2\text{CH}_2\text{CH}_2\text{CH}_2\text{SO}_3^-$

Molecular Weight: 307.5

Aggregation number: 41

Average micellar weight: 12,600

N-Dodecyl-N,N-dimethyl-3-ammonio-1-propanesulfonate



Molecular Formula:  $\text{CH}_3(\text{CH}_2)_{11}\text{N}^+(\text{CH}_3)_2\text{CH}_2\text{CH}_2\text{CH}_2\text{SO}_3^-$

Molecular Weight: 335.5

Aggregation number: 55

Average micellar weight: 18,500

Here again, the molecular weight of these surfactant sulfobetaines are well over 300 daltons and the surfactant sulfobetaines are observed to aggregate in micelles having an overall weight of over 10,000 daltons. These “surfactant” sulfobetaines also include hydrocarbon chains well over six carbon atoms in length. (Gaberc-Porekar Declaration, ¶ 8)

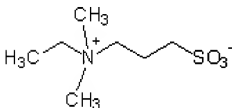
While Miyazawa mentions sulfobetaines, the exact length of the carbon chains in these sulfobetaines is not explicitly stated. However, it is notable that the sulfobetaines referred to in Miyazawa are mentioned at Column 3, lines 23 – 32 and Column 4, lines 32 – 42 along side numerous other surfactants having lauryl (12 carbon) substituents, oleyl (18 carbon) substituents, and stearyl (18 carbon) substituents. From the perspective of a person of ordinary skill in the art, Miyazawa’s reference to surfactant sulfobetaines in this context would have suggested large, micelle-forming sulfobetaine molecules having carbon chains of a similar length. (Gaberc-Porekar Declaration, ¶ 9)

In contrast to the aforementioned surfactant sulfobetaines, Dr. Gaberc-Porekar explains in her Declaration that the non-detergent sulfobetaines (NDSBs) called for in the present claims are relatively small, bipolar compounds containing two oppositely charged polar head groups linked by a short hydrocarbon chain (most commonly a three carbon chain). Due to the relatively short hydrophobic group, such NDSBs cannot aggregate to form micelles. Therefore NDSBs are not considered detergents, hence, the term of art “non-detergent sulfobetaines” or “NDSBs.” In

contrast to detergents, NDSBs are relatively easily separated by dialysis. NDSBs are a type of zwitterionic compound that can enhance the recovery of membrane, nuclear and cytoskeleton-associated proteins and also aid in refolding proteins found in inclusion bodies and bacterial expression systems. NDSBs have also been used in refolding and renaturation of chemically and thermally denatured proteins. (Gaberc-Porekar Declaration, ¶ 10)

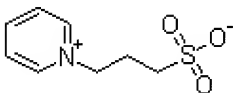
Some typical representative examples of the non-detergent sulfobetaines (NDSBs) include:

Dimethylethylammonium propane sulfonate



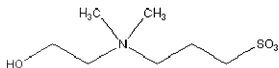
Molecular Weight: 195.3

3-(1-Pyridino)-1-propane sulfonate



Molecular Weight: 201.2

Dimethyl(2-hydroxyethyl)ammonium propane sulfonate



Molecular Weight: 211.3

Once again, these compounds do not form micelles in water and therefore cannot reasonably be considered detergents or surfactants. Such compounds are plainly not suggested

by the reference to “surfactant sulfobetaines” in the Miyazawa reference. (Gaberc-Porekar Declaration, ¶ 11). If anything, Miyazawa suggest the opposite.

In view of the foregoing, it is respectfully submitted that the anticipation rejections based on Miyazawa are clearly not well taken and should be withdrawn.

### III. The Menart Rejections.

The Examiner also contends that Claims 1 – 4, 6, and 8 – 12 are anticipated, under Section 102 (e), by PCT Publication WO 2004/015124 to Menart et al. (“Menart ’124”). The Examiner further contends that Claim 7 would have been obvious from Menart taken in combination with Vuillard.

As Applicants have stressed before, the current claims specify, among other things, a “pharmaceutical composition” suitable for parenteral administration, and which comprises an active pharmaceutical ingredient and a non-detergent sulfobetaine or “NDSB”. In other words, the NDSB is a component of dosage form of a “pharmaceutical composition,” now also clarified as being a material formulated for administration to a subject parentally to make explicit what was already manifestly implicit in the claims as worded before.

This is simply not shown in the Menart reference, and it is certainly not “suggested.” In Menart, an NDSB compound is mentioned only for dissolving so-called “non-classical” inclusion bodies found in cell residue of organisms such as *E. coli*, fermented in a certain way so as to induce formation of the desired inclusion bodies. This disclosure of NDSB as a protein solvent for material recovered from bacterial residue can hardly be said to disclose a “pharmaceutical composition,” much less a pharmaceutical formulation for parenteral administration to a subject.

Since Menart plainly does not disclose at least the aforementioned limitations of Claim 1, it is very apparent that the anticipation rejection of Claim 1 and of its dependent claims based upon Miyazawa is unfounded and contrary to law.

Moreover, and as noted above, Claim 1 has been amended to specify that the pharmaceutical composition comprises an active pharmaceutical ingredient and *from 1 to 1000 mM of a non-detergent sulfobetaine (NDSB)*. In other words, the amount of the NDSB in the pharmaceutical composition is now specified.

This specified concentration range is not specified or even suggested in Miyazawa. Even assuming, for the sake of argument, that the Menart mixture is said to be useful in a final pharmaceutical composition, which it plainly is not, Menart still clearly fails to disclose or suggest the claimed concentration range. These failings of Menart are not cured by adding in Vuillard, which describes nothing that would have suggested what Applicants are claiming, alone or in combination with Menart.

Accordingly, it is respectfully submitted that the anticipation rejections based upon Menart are improper and should be withdrawn. Likewise, the obviousness rejections based upon Menart taken in combination with the Vuillard reference should likewise be withdrawn. The Examiner has failed to show how there would have been any incentive or motivation to combine these references, but even when they are considered in combination, they do not even hint at what Applicants claim.

In light of the foregoing, the present amendment is believed to place the application in a condition for allowance and entry of the foregoing amendments and allowance of the claims is respectfully solicited.

In the event this response is not timely filed, Applicants hereby petition for the appropriate extension of time and request that the fee for the extension along with any other fees which may be due with respect to this paper be charged to our Deposit Account No. **12-2355**.

Respectfully submitted,

LUEDEKA, NEELY & GRAHAM, P.C.

By: /Mark S. Graham/

Registration No. 32,355

MSG:JDG:lal

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P.O. Box 1871  
Knoxville, Tennessee 37901  
(865) 546-4305